EUS pancreatic function testing and dynamic pancreatic duct evaluation for the diagnosis of exocrine pancreatic insufficiency and chronic pancreatitis

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Abstract

Background and Aims: EUS and endoscopic pancreatic function tests (ePFTs) may be used to diagnose minimal- change chronic pancreatitis (MCCP). The impact of evaluation for exocrine pancreatic insufficiency (EPI) and real-time assessment of EUS changes after intravenous secretin on the clinical diagnosis of MCCP is unknown.

Methods: Patients with suspected MCCP underwent baseline EUS assessment of the pancreatic parenchyma and measurement of the main pancreatic duct (B-MPD) in the head, body, and tail. Human secretin 0.2 µg/kg IV was given followed 4, 8, and 12 minutes later by repeat MPD (S-MPD) measurements. Duodenal samples at 15, 30, and 45 minutes were aspirated for bicarbonate concentration. Endoscopists rated the percent clinical likelihood of CP: (1) before secretin; (2) after secretin but before aspiration; and (3) after bicarbonate results.

Results: 145 consecutive patients (mean age 44±13 years; 98F) were diagnosed with EPI (n=32; 22%). S-MPD/B-MPD ratios in the tail 4 and 8 minutes after secretin were higher in the group with normal exocrine function. Ratios at other times, locations and duodenal fluid volumes were similar between the 2 groups. A statistically significant change in the median percent likelihood of CP was noted after secretin in all groups. The sensitivity and specificity of EPI for the EUS diagnosis of CP (≥5 criteria) were 23.4% (95% CI, 12.3-38.0) and 78.6% (95% CI, 69.1-86.2), respectively.

Conclusion: Real-time EUS findings and ePFTs have a significant impact on the clinical assessment of MCCP. The diagnosis of EPI shows poor correlation with the EUS diagnosis of MCCP.

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Introduction

Chronic pancreatitis is an irreversible, fibrosing disease caused most commonly by chronic alcohol or tobacco use, genetic predisposition and recurrent acute pancreatitis.[1] Symptoms almost always include pain and later exocrine pancreatic insufficiency (EPI) with malabsorption may occur with progressive fibrosis. The diagnosis of chronic pancreatitis with extensive calcifications, gland atrophy or pancreatolithiasis is relatively straightforward. However, early or "minimal-change" chronic pancreatitis (MCCP) is more difficult to detect due to the often lack of radiologic findings, laboratory parameters and classic symptomatology. Additional diagnostic tools to permit accurate early detection before extensive fibrosis of the pancreas would be a major advance.

The use of endoscopic ultrasound (EUS) for the diagnosis of chronic pancreatitis has historically used parenchymal and ductal abnormalities[2,3] with diagnostic certainty increasing as more abnormalities are identified. More recently, the Rosemont classification was proposed giving greater weight to some EUS features and assigned major and minor criteria for the diagnosis.[4] However, the use of EUS for diagnosing chronic pancreatitis does have some limitations. First, it is generally accepted that ≥5 EUS features maximizes specificity for the diagnosis but certainty remains less clear in patients with fewer features.[2-6] Second, although EUS findings are speculatively correlated with a histological abnormality, it is unclear which feature is pathologic or seen in normal human aging.[7,8] Third, the relative value of assigning more importance to any EUS criteria remains doubtful over the traditional scoring system.[9] Finally, interobserver agreement for the diagnosis among experts retrospectively using videotaped examinations remains poor.[8]

Hormone-stimulated pancreatic function tests (PFTs) to evaluate for EPI have long been considered the "nonhistological" reference standard for the diagnosis of chronic pancreatitis. Traditionally, these were performed by aspirating fluid from the small bowel after insertion of a double-lumen (Dreiling) collection tube.[10,11] However, use of this tube has largely been replaced by endoscopic PFTs (ePFTs), which use intravenous sedation and a gastroscope to improve patient comfort. Currently used ePFTs with secretin (sPFTs) collect duodenal fluid at timed intervals for at least 45 minutes after hormone administration[12] and use a peak bicarbonate concentration (PBC) of ≤80 mEq/L to diagnosis EPI.[13] Secretin-stimulated ePFTs (sPFTs) provide similar accuracy to PFTs done with the Dreiling tube[14] and demonstrate a sensitivity of 66% to 71% and specificity of 67% to 98% for the diagnosis of chronic pancreatitis.[15-17] Hormone stimulation of pancreatic secretion may also produce variations in main pancreatic duct (MPD) compliance[18,19], duodenal fluid volumes,[17] and possibly sonographic changes in patients with or without chronic pancreatitis or EPI. A small single-center study of 35 patients demonstrated that EUS morphologic evaluation of the pancreas with secretin stimulation (sEUS) and sPFTs can be performed safely simultaneously and MPD compliance may be greater in the pancreatic tail in normal subjects.[19]

In this prospective study, we hypothesized that EUS, sEUS and sPFTs in patients with suspected MCCP could be performed safely in a larger patient population. Secondary objectives were to evaluate differences in duodenal fluid volumes, pancreatic sonographic features and main duct compliance. Finally, we sought to study the sequential impact of findings from EUS alone, sEUS changes and results of sPFTs on the suspected clinical diagnosis of MCCP and the test characteristics of the diagnosis of EPI compared with the EUS diagnosis of MCCP.

Methods

Patient Selection and Study Design

The investigator-initiated protocol was originally intended to be a prospective multicenter study. However the Intuitional Review Board (IRB) at only one invited center (Indiana University Health Medical Center, Indianapolis) approved the protocol and supporting documents (ClinicalTrials.gov Identifier: NCT01997476, registered Nov 13, 2013). After discussion with the senior investigator (T.G.), it was decided to continue as a single-center study. Before enrollment, all patients underwent screening a medical history and physical examination to determine eligibility. Eligible patients signed informed consent before enrollment. Inclusion criteria included patients 18 to 80 years of age with clinical suspicion of chronic pancreatitis with or without EPI in whom ePFTs were planned for structural and functional evaluation of the exocrine pancreas. They were also required to be capable of undergoing sedation and willing/capable of signing informed consent. Exclusion criteria included severe cardiopulmonary or renal disease, ongoing illicit drug use/abuse, moderate to severe alcohol use (<30 grams per day), pregnancy or nursing, known allergy to secretin, use of any medication within the previous 30 days that could cause pancreatitis or interfere with pancreatic function test interpretation, or use of an anticholinergic medication within 48 hours of enrollment. Patients were also excluded with previous pancreatic surgery or sphincterotomy, known pancreatolithiasis or pancreatic calcifications, suspected or proven sphincter of Oddi dysfunction, symptoms of acute pancreatitis within the previous 60 days, a new abdominal pain or exacerbation of chronic pain within 30 days or presence of a condition which may interfere with exocrine pancreatic functioning including (celiac disease, type I diabetes, previous gastrectomy, cystic fibrosis, or severe malnutrition [BMI<18]).

Combined EUS, e-PFT and sEUS Testing Procedure:

All endoscopic procedures were performed by 1 of 3 experienced endosonographers using propofol sedation administered by an anesthesiologist. EGD was initially performed to exclude an alternative cause for symptoms. An electronic radial EUS echoendoscope (Olympus GF-UE160-AL5; Olympus America; Center Valley Pa, USA) assessed for abnormal pancreatic parenchymal (hyperechoic foci ≥2 mm, hyperechoic strands ≥3 mm, lobularity, cysts ≥3mm) and ductal (main duct irregularity, hyperechoic margins, shadowing stones and dilated side branches) findings in the head, body and tail. The baseline main pancreatic duct (B-MPD) diameter was measured in all 3 locations and recorded. Finally, the baseline anteroposterior (B-AP) diameter of the pancreas anterior to the splenoportal confluence was measured. The contents of the gastric and duodenal lumens were then aspirated completely by the echoendoscope and discarded.

Synthetic human secretin (ChiRhoStim; ChiRhoClin Inc, Burtonsville, Md, USA) used for this study is supplied as 16 µg secretin, 1.5 mg of L-cysteine hydrochloride, and 20 mg of mannitol as a lyophilized powder per vial. It was reconstituted in 8 mL of sterile NaCL such that each 1 mL of the resulting solution contains 2 µg of secretin. At study commencement, a test dose of 0.2 µg (0.1mL) test dose was recommended before the full treatment dose to exclude an allergic reaction. If no allergic reaction was noted after one minute, the remaining full dose of secretin 0.2 µg/kg IV was given over 1 minute. During the study, FDA communication removed requirement and thereafter only the full 0.2 µg/kg IV secretin dose was given to remaining study patients.

At 4, 8, and 12 minutes after secretin, real-time dynamic EUS measurement of the secretin-stimulated MPD (S-MPD) was re-measured in the head, body, and tail and any increase in prominence or visibility of parenchymal or ductal features compared with baseline was assessed. Ten minutes after secretin, the

anteroposterior (AP) gland diameter (S-AP) was also re-measured and evaluation of all parenchymal and ductal features were assessed for increased visibility or prominence. After measurements, the echoendoscope was used to aspirate the gastric contents and any residual in the suction tubing were aspirated dry as well. The gastroscope was then placed into the proximal duodenum at or distal to the major papilla. At 15, 30, and 45 minutes after secretin, at least 3mLs of duodenal fluid was attempted to be collected through the suction channel of the gastroscope. The procedure was then completed and the patient brought to recovery. Duodenal collection samples were placed on ice and brought immediately to the hospital chemistry laboratory for evaluation of bicarbonate concentration using the hospital autoanalyzer. No additional therapeutic maneuvers were performed during EUS to minimize confounding variables contributing to potential adverse events.

The endoscopist performing the EUS rated the percent likelihood of chronic pancreatitis clinically at 3 time points during the study: (1) after history, physical examination, and EUS but before secretin; (2) after secretin, repeat pancreatic duct and parenchymal measurements but before duodenal fluid collections, and (3) after all duodenal bicarbonate results were available.

Definitions

The highest bicarbonate concentration from the 3 samples was considered the peak concentration. A peak bicarbonate concentration (PBC) ≥80 mEq/L from secretin ePFT was considered normal. Exocrine pancreatic insufficiency (EPI) was defined as all 3 bicarbonate values <80 mEq/L. The EUS diagnosis of chronic pancreatitis (EUS-CP+) or absence of chronic pancreatitis (EUS-CP-) was defined as the presence of ≥5 parenchymal and/or ductal criteria or ≤4 criteria, respectively.[2,4] Adverse events related to secretin administration and EUS were evaluated. These were classified as (1) expected versus

unexpected; (2) serious adverse event versus important but not serious adverse event; (3) no reasonable possibility (where a medical condition or other cause for the event is identified); and (4) reasonable possibility. Serious adverse events were considered to be any undesirable sign, symptom, or medical condition that was fatal, life-threatening, required inpatient hospitalization ≥24 hours, resulted in persistent or significant disability/incapacity, or was medically significant and which the investigator regarded as serious based on clinical judgement.

Statistical Analysis

Based on previous studies using ERCP as a reference standard, we estimated that the sensitivity and specificity of EUS using ≥5 features of chronic pancreatitis for the detection of EPI was at least 70% and 80%, respectively. Based on these assumptions, enrollment of 800 patients would permit estimation of sensitivity and specificity with confidence limits of 10%. As only one study center (Indiana University Health Medical Center, Indianapolis) approved the protocol and supporting documents, it was decided to continue at that single center study with a suggested enrollment of about 150 patients. This enrollment size is the value that would have been expected from each center recruited from the study outset should approval from all IRBs have been possible.

Analyses were performed to determine associations between outcomes of interest for 2 population groups: (1) Normal exocrine pancreatic function versus EPI and; (2) ≥5 EUS features of chronic pancreatitis (EUS-CP+) vs. ≤4 features of chronic pancreatitis (EUS-CP-). Student t-tests were used to compare continuous variables between groups and Chi-Square tests were used to analyze homogeneity between groups for categorical variables. The Fisher exact test were used to verify the results if numerical values were small. Correlation analyses were performed when analyzing the association between outcome variables of interest, when all were continuous. When data were nonlinear,

nonparametric tests were performed, using the Wilcoxon rank sum test and Spearman's correlation analysis. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

Study Population and Dynamic EUS Measurements

Between December 2013 and November 2017, 169 consecutive patients were evaluated and 5 failed screening due to refusal to take a pregnancy test (n=1), BMI<18 (n=1), previous RYGBP (n=1), use of sandostatin (n=1) and diagnosis of acute pancreatitis (n=1). Of the 164 patients consented, 19 were dropped due to discovery of a pancreatic cyst (suspected IPMN) or solid mass requiring biopsy (n=6), gastric bezoar (n=3), prolonged hypoxia or difficulty with sedation (n=3), inability to complete the procedure due to time constraints or other emergency procedure (n=3), failure to maintain a working IV (n=1), identification of fatty pancreas with nonvisible pancreatic duct (n=1), autoimmune pancreatitis (n=1) and pancreatic calcifications precluding further evaluation of features of chronic pancreatitis (n=1).

The remaining 145 patients (mean age: 44 ± 14 years; 98F) were diagnosed with EPI (n=32; 22%) or normal exocrine pancreatic function (n=131, 78%). The EPI group had a more frequent diagnosis of diabetes (44%) compared those without EPI (16%; p=0.009, Table 1A). Baseline demographics and the frequency of EUS-CP+ (34% vs 32%; p=0.75) were otherwise similar (Table 1B). The ratio of the secretin stimulated main pancreatic duct (S-MPD) to baseline (B-MPD) measurements (S-MPD/B-MPD) in the tail at 4 (p=0.01) and 8 (p=0.02) minutes after secretin were higher in patients with normal exocrine function but were similar at other times and sites in the pancreas. Duodenal fluid quantities aspirated at

all 3 times were also similar between the 2 groups. In 18 patients, the diagnosis of normal exocrine pancreatic function was made only after the 45-minute collection.

Using ≥5 EUS criteria as diagnostic for chronic pancreatitis, 47 out of 145 (32%) were EUS-CP+ whereas the remaining 98 out of 145 (68%) were EUS-CP- (≤4 EUS criteria). Baseline demographics, frequency of EPI, mean S-MPD/B-MPD at all sites and times, mean S-AP/B-AP and duodenal fluid quantities aspirated at all 3 times were also similar between the 2 groups (Table 1B).

Assessment of Parenchymal and Ductal Features after Secretin

During evaluation 10 minutes after secretin, those with normal exocrine pancreatic function (Table 2A) had more visible parenchymal hyperechoic foci (p=0.023), hyperechoic strands (p=0.019) and echogenic main pancreatic duct walls (p=0.002) compared with the EPI group. The remaining parenchymal and ductal changes and the AP gland diameter was similar between the 2 groups. For the EUS-CP+ group, mean gland AP diameter (p=0.03), parenchymal lobularity (p=0.01) and duct sidebranches (p=0.03) were more visible after secretin compared with the EUS-CP- group (Table 2B). The remaining features were similar between the 2 groups.

Endoscopist Clinical Assessment of Likelihood of Chronic Pancreatitis

There were 21 (14%) patients with EPI and EUS-CP- and 77 (53%) with normal exocrine function and EUS-CP-. The remaining were 11 (8%) with EPI and EUS-CP+ and 36 (25%) with normal exocrine function and EUS-CP+. The clinical assessment of the percent likelihood in of chronic pancreatitis in all 4 groups

all 3 time points evaluated is shown in Table 3. For all groups, there was a statistically significant change in the median percent likelihood before, during and after secretin administration.

Performance of Pancreatic Function Testing for the EUS diagnosis of Chronic Pancreatitis

There was no association between the number of EUS criteria identified and the frequency of EPI (p=0.94, Table 4). For the 47 EUS-CP+ patients, 11 (23%) had EPI and 36 (77%) had normal exocrine function. For the 98 EUS-CP- patients, 21 (21%) had EPI and 77 (79%) had normal exocrine function. The diagnosis of EPI had a sensitivity, specificity, positive and negative predictive value and accuracy of 23.4% (95% CI, 12.3-38.0), 78.6% (95% CI, 69.1-86.2), 34.4% (95% CI, 21.6-49.9), 68.1% (95% CI, 63.9-72.1), and 60.7 (95% CI, 52.2-68.7), respectively for the EUS diagnosis of chronic pancreatitis using ≥ 5 criteria (EUS-CP+).

If ≥4 criteria were used for the EUS diagnosis of chronic pancreatitis, there were 67 EUS CP+ patients including 14 (21%) with EPI and 53 (79%) with normal exocrine function. For the 78 EUS-CP- patients, 18 (23%) had EPI and 60 (77%) had normal exocrine function. When ≥4 criteria were used, the diagnosis of EPI had a sensitivity, specificity, positive and negative predictive value, and accuracy of 20.9% (11.9-32.6), 76.9% (66.0-85.7), 43.8% (29.6-59.1), 53.1% (48.8-57.3) and 51.0% (42.6-59.4), respectively for the diagnosis of chronic pancreatitis.

Adverse Events

Three of the 169 (1.7%) consented patients had repeated or prolonged hypoxia requiring early termination of the procedure and were therefore excluded from data analysis. None of the 3 required

application of positive pressure ventilation and were classified as expected, important but not serious adverse events

Discussion

In the current study, we found that same session EUS morphologic evaluation, dynamic measurement of MPD compliance (sEUS) and collection of duodenal fluid (sPFTs) were feasible and safe in a large prospective single center cohort. These results confirm findings of a previous smaller study.[19] Furthermore, parenchymal and ductal findings from sEUS and duodenal bicarbonate findings from ePFTs had a significant impact on the clinical diagnosis of chronic pancreatitis in patients with and without EUS-CP (≥5 features). To our knowledge, this is the first prospective evaluation of the impact of ePFT findings on the clinical suspicion of chronic pancreatitis in these patients.

Administration of secretin and resultant increase in pancreatic fluid secretion would theoretically increase MPD diameter in and duodenal fluid volume in normal subjects. MPD compliance[20-22] and duodenal (pancreatic) fluid volume measurements[17,23] after secretin have therefore been evaluated as alternative measures for exocrine pancreatic function. Gardner et al[19] found that duct compliance measured by EUS was higher in the pancreatic tail after secretin in normal subjects. Similarly, we found that the duct compliance (S-MPD/B-MPD) was higher in the pancreatic tail at 4 and 8 minutes (but not 12 minutes) after secretin in those with normal exocrine function compared with the EPI group. However, there was no difference in duct compliance in the head or body at any time after secretin between these 2 groups and also no difference in duct compliance in the head, body or tail in the EUS-CP+ compared the EUS-CP- group. Furthermore, duodenal volumes aspirated at 15, 30 and 45 minutes after secretin were the same in all groups. These findings suggest that EUS measurement of duct

compliance and duodenal volumes after secretin may not be useful for the diagnosis of EPI or chronic pancreatitis.

Early research noted that output from the pancreas peaked 30 minutes after hormone stimulation.[24-26] Thus, sampling from duodenal fluid by the Dreiling tube to test physiologic function typically occurred up to 60 minutes after stimulation.[27,28] Current variations of ePFTs include testing only up to 45 minutes after secretin[12] or administering secretin 30 minutes before sedation for endoscopy.[17] In the current study, the first collection occurred 15 minutes after sedation in order to complete EUS morphologic evaluation after secretin (sEUS exam) but continued to 45 minutes to ensure that PBC is approximated. We found that in 18 patients, the diagnosis of normal exocrine function was made only by the results of the 45-minute collection, which confirm the necessity of this timed collection during ePFTs.

Because MRI with IV contrast may produce or detect abnormalities such as signal differences on T1 imaging, gland atrophy and irregular outer margins[23,29], we postulated that the pancreatic duct and parenchyma may produce sonographic changes after secretin. In patients with normal exocrine function, post-secretin imaging showed parenchymal hyperechoic foci and strands and MPD echogenic walls were more visible compared with the EPI group. For the EUS-CP+ group, parenchymal lobularity and duct sidebranches were more visible after secretin compared with the EUS-CP- group. These findings may represent sonographic imaging of increased fluid secretion from ductal cells but as noted above these changes did not generally translate into differences in duct compliance or duodenal volumes sampled in patients with or without EPI or EUS-CP.

The development of pancreatic fibrosis in alcoholics appears to be patchy and may develop before the clinical onset of chronic pancreatitis.[30] This preclinical stage of pancreatic disease before chronic pancreatitis has been termed pancreatopathy[31] and may manifest histology as parenchymal atrophy and acinar cell loss. The absence of clinical symptoms may eventually lead to minimal-change chronic pancreatitis (MCCP) which is chronic pancreatitis in patients with abdominal pain but equivocal or absent related imaging findings.[32] The findings of histology in evaluation of pancreatic disease is usually impractical unless patients undergo surgery or preoperative biopsy.[33] Therefore, we attempted to use both EUS and sPFTs to identify patients with MCCP. Previous studies evaluating sPFTs demonstrate a sensitivity of 66% to 71% and specificity of 67-98% for the diagnosis of chronic pancreatitis (Table 5) compared with a reference standard of ≥4 EUS criteria[15], histopathology[16] or clinical consensus.[17] We found that the diagnosis of EPI had a sensitivity, specificity and accuracy of 23.4%, 78.6% and 60.7%, respectively compared with the EUS diagnosis of chronic pancreatitis using ≥5 criteria (EUS-CP+). If only ≥4 criteria, the diagnosis of EPI had a sensitivity, specificity and accuracy of 20.9%, 76.9% and 51.0%, respectively. For the current study, we estimated that the sensitivity and specificity of EUS using ≥5 features of chronic pancreatitis for the detection of EPI was at least 70% and 80%, respectively when using ERCP as a reference standard. Our findings are significantly lower than previously reported and likely explained by overdetection and mislabeling of abnormal parenchymal and ductal features in normal patients or those with MCCP and the lack of inclusion of patients with advanced disease. This phenomenon has also been described for interpretation of pancreatograms during ERCP.[34] A recent study highlighted the difficulty of EUS in the evaluation of histology findings in noncalcific chronic pancreatitis. Trikudanathan et al[32] found that compared with histology before total pancreatectomy and islet autotransplantation (TPIAT), identification of ≥4 EUS chronic pancreatitis features within 1 year of surgery showed a sensitivity, specificity and accuracy of 61%, 75%, and 63% for the histologic diagnosis of chronic pancreatitis. These data along with the current study suggest that use of EUS alone

for the diagnosis of MCCP should be discouraged and instead used along with direct testing for EPI such as ePFTs. In our study, findings from ePFTs did increase the clinical diagnosis of chronic pancreatitis in all subgroups evaluated. A normal EUS exam alone may be sufficient alone to exclude chronic pancreatitis whereas findings of advanced disease (pancreatolithiasis and calcifications) is sufficient to confirm the diagnosis.

We found that in EUS-CP+ and EPI were diagnosed concomitantly in 11 (8%) patients whereas EUS-CP- and normal exocrine function were found concomitantly in 77 (53%) patients, which led to median final certainties of chronic pancreatitis of 90% and 0%, respectively. The remaining 57 (39%) patients had discordant findings between EUS and sPFT results which led to difficulty and wide-ranging certainties for the clinical diagnosis of chronic pancreatitis. It is crucial that endoscopists who perform EUS and ePFTs are aware of these possible discrepancies and how they may impact clinical management. Further research is required to evaluate the test characteristics of EPI for the diagnosis of chronic pancreatitis using other gold standards besides EUS findings.

Our study is the first to prospectively evaluate sonographic findings of chronic pancreatitis after secretin and the impact of sEUS and ePFT findings on the subsequent clinical diagnosis. Nevertheless, our study does have 3 principal limitations. First, the study population was smaller than designed because IRB approval was only able to be obtained at one of the original participating institutions. Thus, study findings must be interpreted with caution as the sample size was only about one-fifth of the intended figure of 800 based on power calculations. However, this study is still the largest study to date the prospectively evaluates ePFTs and EUS and used 3 different endosonographers. We believe it is unlikely that this study will be replicated in a larger group. The second limitation is the use of EUS features of

chronic pancreatitis as the gold standard for the diagnosis of chronic pancreatitis. Although other studies have used histology, clinical follow-up, or ERCP and MRCP findings, our study design in patients with MCCP did not permit use of other surrogate tests. Finally, interpretation of pancreatic duct and parenchymal effects of secretin was not performed by endosonographers blinded to the previous ultrasound findings. ‘

In conclusion, same session EUS and ePFTs are safe and feasible. Secretin causes distinct sonographic changes in patients with normal exocrine function and EUS evidence of chronic pancreatitis but dynamic MPD ratios and duodenal volumes aspirated after secretin do not appear useful for the diagnosis of EPI. Findings from sEUS and ePFTs have a significant impact in the clinical assessment chronic pancreatitis in patients with and without EUS-CP but ePFT results show poor correlation to the EUS diagnosis of chronic pancreatitis. Finally, a 45-minute ePFT collection is required to confirm the diagnosis of normal exocrine function. Further studies, particularly in those with suspected MCCP are required to evaluate the role of EUS and ePFTs.

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Table 1A: Baseline Demographic and Clinical Data and Results of Dynamic EUS Measurements and Pancreatic Fluid Collection Before and After Secretin for the 145 patients with Exocrine Pancreatic Insufficiency (n=32) and Exocrine Pancreatic Sufficiency (n=113)

	Overall (n=145)	Exocrine Pancreatic Insufficiency (n=32)	Normal exocrine pancreatic function (n=113)	p-value
Mean Age (SD)	44.0 (13.5)	47.8 (13.6)	43.0 (13.3)	0.07
Female (n, %)	98 (68.1)	24 (75.0)	74 (66.1)	0.34
Median (range) BMI (kg/m^2)	26.3 (15.2 – 52.3)	29.1 (19.1 – 40)	25.9 (15.2 – 52.3)	0.09
Tobacco User (n, %)	59 (41.0)	15 (46.9)	44 (39.3)	0.44
Alcohol (n, %)	17 (11.8)	4 (12.5)	13 (11.6)	0.89
Diabetic (n. %)	32 (22.2)	14 (43.8)	18 (16.1)	0.0009
Number of EUS features for chronic pancreatitis (n, %)				
≤4 ≥5	98 (67.6) 47 (32.4)	21 (65.6) 11 (34.4)	77 (68.1) 36 (31.9)	0.79
Mean (SD) S-MPD/B-MPD				

Head at 4 minutes	1.30 (1.19)	1.28 (0.33)	1.30 (1.34)	0.87
Body at 4 minutes	1.35 (0.43)	1.34 (0.44)	1.36 (0.42)	0.83
Tail at 4 minutes	1.31 (0.47)	1.12 (0.37)	1.36 (0.49)	0.01
Head at 8 minutes	1.31 (1.36)	1.21 (0.29)	1.33 (1.53)	0.41
Body at 8 minutes	1.25 (0.40)	1.29 (0.55)	1.24 (0.35)	0.59
Tail at 8 minutes	1.32 (0.46)	1.18 (0.32)	1.36 (0.49)	0.02
Head at 12 minutes	1.32 (0.62)	1.26 (0.31)	1.33 (1.82)	0.67
Body at 12 minutes	1.24 (0.40)	1.25 (0.40)	1.24 (0.40)	0.85
Tail at 12 minutes	1.28 (0.42)	1.23 (0.40)	1.29 (0.43)	0.44
Mean (SD) S-AP diameter/ B-AP diameter	1.05 (0.65)	1.03 (0.17)	1.06 (0.73)	0.67
Mean (SD) HC03 (mmol/L) at 15 minutes	75.1 (18.3)	57.1 (16.8)	80.2 (15.3)	<.0001*
Mean (SD) HCO_3 (mmol/L) at 30 minutes	80.9 (19.7)	59.2 (19.1)	87.1 (14.9)	<.0001*
Mean (SD) HCO_3 (mmol/L) at 45 minutes	82.3 (18.3)	58.8 (17.4)	89.0 (11.9)	<.0001*
Mean (SD) Volume (mL) duodenal fluid at 15 minutes	11.8 (6.4)	13.1 (7.6)	11.4 (6.0)	0.18
Mean (SD) Volume (mL) duodenal fluid at 30 minutes	11.9 (6.3)	11.3 (6.3)	12.1 (6.3)	0.49
Mean (SD) Volume (mL) duodenal fluid at 45 minutes	10.9 (7.3)	11.3 (8.7)	10.8 (6.9)	0.71

Abbreviations: EUS: endoscopic ultrasound; BMI: body mass index; MPD: main pancreatic duct; HC03: bicarbonate

Footnote: Exocrine pancreatic insufficiency (EPI) was defined as all bicarbonate values <80 mEq/L. Normal exocrine pancreatic function had at least one value >80mEq/L. The EUS diagnosis of chronic pancreatitis (EUS-CP+) or absence of CP (EUS-CP-) was defined as the presence of ≥5 parenchymal or ductal criteria or ≤4 criteria, respectively.

Table 1B: Baseline Demographic and Clinical Data and Results of Dynamic EUS Measurements and Pancreatic Fluid Collection Before and After Secretin for the 145 patients with EUS evidence of chronic pancreatitis (≥5 criteria, EUS-CP+) and ≤4 criteria (EUS-CP-)

	EUS-CP+ (n=47)	EUS-CP- (n=98)	p-value
Mean (SD) Age	44 (14.5)	44 (13.0)	0.99
Female (n, %)	30 (65.2)	68 (69.4)	0.62
Median (range) BMI (kg/m^2)	26.6 (17.3 – 52.3)	26.2 (15.2 – 47.1)	0.88
Tobacco User (n, %)	22 (47.8)	37 (37.8)	0.25
Alcohol (n, %)	6 (13.0)	11 (11.2)	0.75
Diabetic (n. %)	10 (21.7)	22 (22.5)	0.92
Exocrine Pancreatic Insufficiency (n, %)	11 (23.4)	21 (21.4)	0.79
Mean (SD) S-MPD/B-MPD			
Head at 4 min	1.2 (0.3)	1.4 (1.4)	0.31
Body at 4 min	1.3 (0.4)	1.4 (0.4)	0.26

Tail at 4 min	1.3 (0.5)	1.3 (0.5)	0.30
Head at 8 min	1.4 (0.3)	1.3 (1.7)	0.60
Body at 8 min	1.3 (0.4)	1.2 (0.4)	0.39
Tail at 8 min	1.4 (0.5)	1.3 (0.5)	0.39
Head at 12 min	1.2 (0.3)	1.4 (2.0)	0.46
Body at 12 min	1.27 (0.4)	1.23 (0.4)	0.52
Tail at 12 min	1.33 (0.4)	1.3 (0.5)	0.32
Mean (SD) S-AP diameter/ B-AP diameter	1.02 (0.1)	1.07 (0.8)	.053
Mean (SD) $HC0_3$ (mmol/L) at 15 minutes	74.70 (21.8)	75.3 (16.5)	0.88
Mean (SD) HCO_3 (mmol/L) at 30 minutes	81.15 (23.4)	80.7 (17.8)	0.93
Mean (SD) HCO_3 (mmol/L) at 45 minutes	80.04 (22.1)	83.42 (16.1)	0.35
Mean (SD) Volume (mL) duodenal fluid at 15 minutes	12.26 (6.2)	11.51 (6.5)	0.51
Mean (SD) Volume (mL) duodenal fluid at 30 minutes	12.26 (6.4)	11.79 (6.3)	0.68
Mean (SD) Volume (mL) duodenal fluid at 45 minutes	11.06 (6.1)	10.81 (7.9)	0.84

Abbreviations: EUS: endoscopic ultrasound; BMI: body mass index; MPD: main pancreatic duct; HC03: bicarbonate

Exocrine pancreatic insufficiency (EPI) was defined as all bicarbonate values <80 mEq/L. Normal exocrine pancreatic function had at least one value >80mEq/L. The EUS diagnosis of chronic pancreatitis (EUS-CP+) or absence of CP (EUS-CP-) was defined as the presence of ≥5 parenchymal or ductal criteria or ≤4 criteria, respectively.

Table 2A: EUS Pancreatic Parenchymal and Ductal Changes after Human Secretin in Patients with and without Exocrine Pancreatic Sufficiency and Exocrine Pancreatic Insufficiency

	Exocrine pancreatic insufficiency (n=32)	Normal exocrine pancreatic function (n=113)	*P* value
Increased Parenchymal Features Visible After Secretin (n, %)			
Hyperechoic Foci	12 (38)	68 (60)	0.023
Hyperechoic Strands	13 (41)	72 (64)	0.019
Cysts	1 (3)	2 (2)	0.53
Lobularity	1 (3)	9 (8)	0.46
Increased Ductal Features Visible After Secretin (n, %)			
Hyperechoic walls	4 (13)	48 (43)	0.002
Sidebranches	11 (34)	39 (35)	0.99

Diameter	1 (3)	2 (2)	0.53
Irregularity	0 (0)	0 (0)	n/a
Stones	1 (3.1)	0 (0)	0.22
Mean (SD) AP diameter (mm)	15.8 (3.1)	15.9 (3.7)	0.79

Definitions:

Exocrine pancreatic insufficiency (EPI) was defined as all bicarbonate values <80 mEq/L.
Normal exocrine pancreatic function had at least one value >80mEq/L

Table 2B: EUS Pancreatic Parenchymal and Ductal Changes After Secretin in Patients with EUS-CP+ (≥5 criteria) and without EUS-CP- (≤4 criteria)

	EUS-CP (+) (n=47)	EUS-CP (-) (n=98)	*P* value
Increased Parenchymal Features Visible After Secretin (n, %)			
Hyperechoic Foci	26 (55)	54 (55)	0.98
Hyperechoic Strands	28 (60)	57 (58)	0.87
Cysts	0 (0)	3 (3)	0.55
Lobularity	7 (15)	3 (3)	0.01
Increased Ductal Features Visible After Secretin (n, %)			
Hyperechoic Margins	20 (43)	32 (33)	0.26
Dilated Sidebranches	22 (47)	28 (29)	0.03
Diameter	1 (2)	2 (2)	1.0

Main duct irregularity	0 (0)	0 (0)	n/a
Intraductal Stones	0 (0)	1 (1)	1.0
Mean (SD) Anteroposterior (AP) diameter (mm)	16.8 (3.5)	15.5 (3.5)	0.03

Table 3: Endoscopist Assessment of Percent Certainty of Chronic Pancreatitis (CP) Pre-secretin, Post-Secretin and After Duodenal Bicarbonate Results (Final Certainty) in Patients with Exocrine Pancreatic Insufficiency (EPI), Normal Exocrine Pancreatic Function and EUS criteria with (EUS-CP+) or without (EUS-CP-) evidence of Chronic Pancreatitis.

Final Diagnosis	**Median Pre-Secretin Certainty of CP (%, range)**	**Median Post-Secretin/Pre-sPFTs Certainty of CP (%, range)**	**Median Final Certainty of CP after sPFTs (%, range)**	***P* value**
EUS-CP(-) and EPI (n=21)	0 (0 – 50)	20 (0 – 50)	70 (20 – 100)	0.009

EUS-CP(-) and Normal exocrine pancreatic function (n=77)	20 (0-75)	20 (0 – 100)	0 (0-100)	0.028
EUS-CP(+) and EPI (n=11)	60 (20 – 100)	60 (20 – 100)	90 (80 – 100)	.023
EUS-CP(+) and Normal exocrine pancreatic function (n=36)	60 (15 – 100)	57.5 (20 – 100)	32.5 (0-100)	0.0009

Note: The endoscopist performing the EUS rated the percent likelihood of CP clinically at 3 time points during the study: 1) Pre secretin: after history, physical exam and EUS but before secretin administration; 2) Post Secretin/Pre-sPFTs: After secretin administration with repeat pancreatic duct and parenchymal sonographic assessment but before timed duodenal fluid collections and; 3) Final: after all duodenal bicarbonate results were available.

Abbreviations: EUS – endoscopic ultrasound; HC03- bicarbonate; PPV- positive predictive value; NPV – negative predictive value

Definitions:

Exocrine Pancreatic Insufficiency (EPI): Peak Bicarbonate Concentration <80mEq/L

Normal exocrine pancreatic function: Peak Bicarbonate Concentration ≥80mEq/L

EUS findings of Chronic Pancreatitis (EUS-CP+): ≥5 criteria.

EUS findings of no Chronic Pancreatitis (EUS-CP -): <4 criteria

Table 4: Relationship between Number of EUS Criteria for Chronic Pancreatitis for the 145 patients with Exocrine Pancreatic Insufficiency (n=32) and Exocrine Pancreatic Sufficiency (n=113)

	Overall (n=145)	Exocrine Pancreatic Insufficiency (n=32)	Normal exocrine pancreatic function (n=113)	*P* value
Number of EUS criteria for the Diagnosis of Chronic Pancreatitis (n, %)				
0	13 (9.0)	3 (9.4)	10 (8.9)	.9367
1	4 (2.8)	2 (6.3)	2 (1.8)	
2	25 (17.2)	5 (15.6)	20 (17.7)	
3	36 (24.8)	8 (25.0)	28 (24.8)	
4	20 (13.8)	3 (9.4)	17 (15.0)	

5	30 (20.7)	7 (21.9)	23 (20.4)	
6	11 (7.8)	3 (9.4)	8 (7.1)	
7	5 (3.5)	1 (3.1)	4 (3.5)	
8	0 (0)	0 (0)	0 (0)	
9	1 (0.7)	0 (0)	1 (0.9)	

Definitions:

Exocrine Pancreatic Insufficiency (EPI): Peak Bicarbonate Concentration <80mEq/L

Normal exocrine pancreatic function: Peak Bicarbonate Concentration ≥80mEq/L

Figure 1: Endoscopist Assessment of Percent Certainty of the Clinical Diagnosis of Chronic Pancreatitis (CP) at 3 different time points: pre-secretin, post-secretin and after duodenal bicarbonate results (final) in patients with EUS-CP+ (≥5 criteria), EUS-CP- (≤4 criteria), Exocrine Pancreatic Insufficiency and Exocrine Pancreatic Sufficiency

Definitions:

Exocrine Pancreatic Insufficiency (EPI): Peak Bicarbonate Concentration <80mEq/L

Normal exocrine pancreatic function: Peak Bicarbonate Concentration ≥80mEq/L

EUS findings of Chronic Pancreatitis (EUS-CP+): ≥5 criteria.

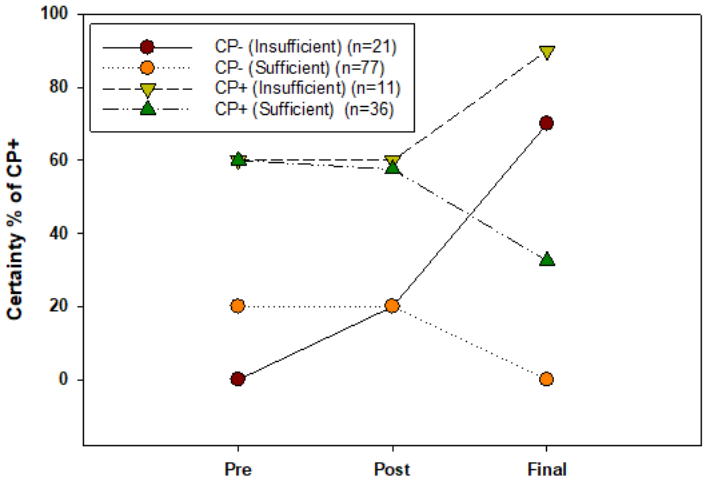
EUS findings of no Chronic Pancreatitis (EUS-CP -): <4 criteria

Table 5: Published Studies Evaluating the Test Characteristics of Endoscopic Pancreatic Function Tests (ePFTs) with Secretin for the Diagnosis of Chronic Pancreatitis.

Author (yr)	Reference	N	Study Design	HC03 collection times after secretin (minutes)	Reference standard for diagnosis of chronic pancreatitis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Stevens (2009)	15	50	Single center, prospective	15, 30, 45	≥4 EUS criteria	71	92	NR	NR	NR
Albashir (2010)	16	25	Single center, retrospective	15,30, 45,60	Histopathology	86	67	NR	NR	NR
Lara (2017)	17	81	Multicenter, retrospective	35, 40, 45, 50	Clinical Consensus of Available Studies	66	98	94.7	85.5	NR
Current Study	--	145	Single center, prospective	15, 30, 45	≥5 EUS criteria	23.4	78.6	34.4	68.1	60.7

Note: All studies cited use a Peak Bicarbonate Concentration <80mEq/L for the Diagnosis of Exocrine Pancreatic Insufficiency

Abbreviations: ePFTs: endoscopic pancreatic function tests; EUS – endoscopic ultrasound; HC03- bicarbonate; PPV- positive predictive value; NPV – negative predictive value


CP- (Insufficient) (n=21)
CP- (Sufficient) (n=77)
CP+ (Insufficient) (n=11)
CP+ (Sufficient) (n=36)
Certainty % of CP+
100
80
60
40
20
0
Pre
Post
Final

Acronyms

AP: anteroposterior

BMI: body mass index

ePFTs: endoscopic pancreatic function tests

EPI: exocrine pancreatic insufficiency

EUS: endoscopic ultrasound

EUS-CP+: EUS diagnosis of chronic pancreatitis

EUS-CP-: absence of EUS diagnosis of chronic pancreatitis

MPD: main pancreatic duct;

HC03: bicarbonate

MCCP: minimal-change chronic pancreatitis

MRI: magnetic resonance imaging

PBC: peak bicarbonate concentration

RYGBP: Roux-en-Y gastric bypass

sPFTs: secretin stimulated endoscopic pancreatic function tests

S-MPD/B-MPD: secretin main pancreatic duct diameter/baseline main pancreatic duct diameter

SAE: serious adverse event